CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

PHOSPHAMIDON

Chemical Code # 000482, Tolerance # 00239
SB 950 # 099

October 26, 1987
Revised 8/11/88, 8/29/89, 7/13/90

I. DATA GAP STATUS

Combined (chronic + onco) rat :	No data gap, no adverse effect
Chronic dog :	No data gap, no adverse effect
Onco rat:	See combined rat
Onco mouse :	Data gap, inadequate study, no adverse effect indicated
Repro rat :	No data gap, no adverse effect
Terato rat :	No data gap, no adverse effect
Terato rabbit :	No data gap, no adverse effect
Gene mutation :	No data gap, no adverse effect
Chromosome :	No data gap, possible adverse effect
DNA damage :	No data gap, no adverse effect
Neurotoxicity :	No data gap, no adverse effect

Toxicology one-liners are attached.

** indicates acceptable study
Bold face indicates possible adverse effect
File name : T900713
Toxicology summary by J. Gee; revised 8/88 by M. Silva, 8/89 G. Chernoff, 7/90 Kishiyama & Silva.

Record numbers through volume 239-030 listed by the Pesticide Registration Library have been rectified with those listed in the Toxicology Summary.

EPA's view of Phosphamidon is presented in the EPA Reregistration Standard (12/87).

II. TOXICOLOGY SUMMARY

COMBINED (ONCO + CHRONIC), RAT

** 008 052101 "Twenty Four Month Combined Chronic Oral Toxicity and Oncogenicity Study in Rats Utilizing Phosphamidon", (American Biogenics Corp., Decatur, IL., # 410-1056, 2/28/86), Phosphamidon Technical 91.8%, was administered in diet to Crl: COBS CD (SD) BR rats (20/sex for the chronic subgroup and 60 or 70/sex for the oncogenicity subgroup) for 24 months at 0, 1, 30, or 80 ppm (2 additional dose levels 0.2 and 0.8 were terminated after 15 weeks). Decreased bodyweight gain in males at 80 ppm throughout the study, decreased gain in females early in study but comparable by week 15. Serum and brain cholinesterase inhibition in both sexes at 30 and 80 ppm. No adverse effects. NOEL = 1 ppm (cholinesterase inhibition, irritability with sequella in dermatitis in both sexes). Onco NOEL $\geq$ 80 ppm. ACCEPTABLE. (Green, 9/30/87 and Gee, 10/14/87).

EPA Guideline: Cholinesterase inhibition in serum and brain; NOEL=1 ppm

019 063183. Supplement to 052101. This volume contains historical data. (Kishiyama, 11/20/89).

CHRONIC, RAT

See combined rat.

CHRONIC, DOG

** 029 070123, "One-Year Chronic Oral Toxicity Study in Beagle Dogs", (W. Kobel, DVM; CIBA-GEIGY Limited, Laboratory Study No. 820753. 2/4/85). Phosphamidon technical (C 570 technical; purity = 91.8%; LOT #: p. 13449) was administered orally, in gelatine capsules, at 0 (vehicle = diet only or possibly empty gelatine capsule), 0.05, 0.1, and 2.5 mg/kg to Beagle dogs (4/sex/group for the Main Group, 2/sex/group for Interim Sacrifice and 2/sex in the control and high dose for the Recovery Group) for 1 year. **No adverse effect.** NOEL $\geq$ 2.5 mg/kg (no significant chronic toxicity was observed at any dose). Nominal ChE NOEL = 0.1 mg/kg (plasma ChE in females throughout the study, erythrocyte ChE in both sexes at $\geq$ 13 weeks and brain ChE in females at 52 weeks was significantly depressed). **ACCEPTABLE.** (Kishiyama & Silva, 4/26/90).

027 070120. This volume contains a summary of 070121 & 070123 (no worksheet). (Kishiyama & Silva, 5/10/90).

SUBCHRONIC, RABBIT

** 028 070121, "21-Day Dermal Toxicity Study in Rabbits", (Khun, J.O., Ph.D., Stillmeadow, Inc., Laboratory Study No. 4701-87, 12/30/88). Phosphamidon technical (purity = 92.1%; LOT #: FL 851179; opaque, dark brown liquid; density 1.28 mg/ml) was administered dermally at 0 (no vehicle used), 10, 100, or 1000 (reduced to 750 mg/kg after day 13) mg/kg/day to 5 New Zealand white rabbits/sex/dose (5x/week for 3 weeks--15 days total). 130 days later, 0 (deionized water), 0.1, or 1.0 mg/kg/day of phosphamidon technical was administered to 5 rabbits/sex/dose on the same treatment schedule as the first experiment. **No adverse effect**. Systemic NOEL = 100

mg/kg/day (subacute superficial dermatitis and erythema/edema were observed in both sexes). ChE NOEL > 1.0 < 10 mg/kg/day (significant inhibition of brain cholinesterase activity was observed in both sexes at ≥ 10 mg/kg/day). ACCEPTABLE. This study contains supplemental data. (Kishiyama & Silva, 4/30/90).

027 070120. This volume contains a summary of 070121 and 070123 (no worksheets). (Kishiyama & Silva, 5/1/90).

ONCOGENICITY, RAT

018 927490 "Bioassay of Phosphamidon for Possible Carcinogenicity, CAS No. 13171-21-6", (Carcinogenesis Testing Program, 8/78). Phosphamidon technical (purity not stated) was administered in diet to Osborne-Mendel rats at 0, 80 and 160 ppm (50 rats/sex/group) for 80 weeks, then observed without compound administration for 30 or 31 weeks. Matched controls consisted of 10 untreated rats/sex; pooled controls were matched controls combined with 85/sex from similar bioassays of 8 other chemicals. The study was initially considered to have an adverse effect (J. Wong, 4/17/85; J. Gee, 10/22/87) based on the apparent increase in oncogenic effect of phosphamidon. Upon re-evaluation (M. Silva, 7/28/88), it was decided that based on historical data the tumor incidences observed in both sexes were not significantly increased over expected values. Therefore, there was no adverse effect indicated**.** NOEL < 80 ppm (decreased weight gain and generalized tremors in both sexes; apparent increased incidence in hemangiomas, hemangiosarcomas in males and C-cell adenomas or carcinomas in both sex--within historical range). NOT ACCEPTABLE (purity of test article not stated; too few animals in the control group; only 2 dose levels tested; animals should have been weighed weekly for the 1st 13 weeks; weights were not taken on liver, kidneys, brain and testes; histopathology was not performed on all required tissues; no individual data were provided; no blood work was done). Possibly upgradeable (individual data and purity of test article must be provided). (M. Silva, 7/28/88).

EPA one-liner: High incidence of tumors in both historical and matched controls from animals (Osborne-Mendel rats) in this laboratory made assessment difficult: Males - Hemangiomas and hemangiosarcomas of the spleen. Females - C-cell adenomas and carcinomas of the thyroid.

001 927490 This is the same study as 018 927490 but was submitted by a different registrant. (M. Silva, 7/29/88).

ONCOGENICITY, MOUSE

018 038437 "Bioassay of Phosphamidon for Possible Carcinogenicity, CAS No. 13171-21-6", (Carcinogenesis Testing Program, 8/78). Phosphamidon technical (purity not stated) was administered in diet to B6C3F1 mice at 0, 80 and 160 ppm (50 mice/sex/group). Males (at 80 ppm) were treated for 71 weeks, then observed for 19 weeks, or (at 160 ppm) males were fed for 62 weeks, then observed for 28 weeks. Females (at 80 & 160 ppm) were fed for 80 weeks, then observed for 10-11 weeks. Matched controls consisted of groups of 10 untreated mice/sex; pooled controls were matched controls combined with 80/sex from similar bioassays of 8 other chemicals. The study was initially considered to show an adverse effect based on the "poor physical" appearance of the male mice (J. Wong, 4/17/85). Upon re-evaluation (J. Gee, 10/22/87) it was decided the report was inadequate to judge the cause of this effect and since no oncogenic effect was found in either sex, the result was changed to no adverse effect indicated**.** NOEL = 80 ppm (decreased body weight gain and tremors in both sexes). No oncogenic effects were observed with phosphamidon. NOT ACCEPTABLE (purity of test article not stated; too few animals in the control group; only 2 dose levels tested; animals should have been weighed

weekly for the 1st 13 weeks; weights were not taken on liver, kidneys, brain and testes; histopathology was not performed on all required tissues; no individual data were provided; no blood work was done). Possibly upgradeable (individual data and purity of test article must be provided). (M. Silva, 7/28/88).

EPA one-liner: Negative for carcinogenicity (B6C3F1 mice) - Hyperexcitability and tremors seen at both treatment levels (80 and 160 ppm). EPA considers the mouse oncogenicity to be inadequate.

001 038437 This is the same study as 018 038437 but it was submitted by a different registrant.

REPRODUCTION, RAT

** 007 052100 "Two-Generation Reproduction Study of Phosphamidon Technical in Albino Rats", (Science Applications, Inc., La Jolla, CA., 1/25/85), Phosphamidon Technical 92.1% purity, lot numbers FL821262 and FL832035, fed in the diet for 2 generations, 2 litters/generation, 15 males/level and 29 or 30 females/level at 0, 5, 30, or 50 (reduced from 80 ppm 2 weeks into the study) ppm. Tremors, ocular and nasal discharges, unthriftiness, and hyperactivity at 30 and 50 ppm. Decreased bodyweights in parental F1 and weanling F1b males at 30 and 50 ppm and in females at 50 ppm. No adverse effects. Nominal systemic maternal NOEL = 5 ppm; reproduction NOEL = 30 ppm (decreased survival to day 21 reduced weight gain). ACCEPTABLE. (Green, 9/29/87 and Gee, 10/15/87)

EPA Guideline: Parental NOEL=30 ppm; Reproductive/Developmental NOEL=5 ppm

TERATOLOGY, RAT

** 005 052098 "Teratology Study of Phosphamidon Technical in Rats", (Science Applications, Inc., La Jolla, CA., 1/24/85), Phosphamidon Technical, 91.8% purity, lot # FL831147, administered by gavage, 30/dose, on days 6 through 15 of gestation (presence of vaginal smear or plug = 0) at 0 (0.2% CMC), 1, 2, or 4 mg/kg. Tremors, hypoactivity, and oral and ocular discharges at 2 and 4 mg/kg. Reduced maternal weight gain at 4 mg/kg. Increased number of fetuses classified as runt (bodyweight 30% less than mean control) at 4 mg/kg. NOEL (maternal) = 1 mg/kg, (developmental) = 2 mg/kg. No adverse effects. Initially reviewed as unacceptable but upgradeable with submission of dosing solution analysis or records of preparation and retrospective analysis (Green 9/25/87 and Gee 10/19/87). The data provided in the report on the dosing solution (CDFA record no. 075500) are adequate to complete the study which has been upgraded to ACCEPTABLE status (Chernoff, 8/29/89).

** 006 052099 "Teratology Study of Phosphamidon Technical in Rats", (Science Applications, Inc., La Jolla, CA., 1/24/85), Phosphamidon Technical 92.1% purity, lot # FL832035, administered by gavage, 30/level, on days 6 through 15 of gestation (presence of vaginal smear or plug = 0) at 0 (0.2% CMC), 0.5, 2, 4, or 6 mg/kg. Tremors, salivation, ocular and anal discharges at 2, 4 and 6 mg/kg. Reduced maternal weight gain at 2 and 4 mg/kg. 5/30 and 24/30 deaths at 4 and 6 respectively. Increased number of fetuses classified as runt (bodyweight 30% less than mean control) at 4 mg/kg. No adverse effects. NOEL (maternal) = 0.5 mg/kg, (developmental) = 2 mg/kg. Initially reviewed as unacceptable, but upgradeable with the submission of analysis of dosing solutions or records of preparation and retrospective analysis (Green 9/28/87 and Gee 10/19/87). The data provided in the report on the dosing solution (CDFA record no. 075500) are adequate to complete the study which has been upgraded to ACCEPTABLE status (Chernoff, 8/29/89).

030 075500 A supplementary report dated July 89, with analytical data for the dosing solutions used in teratology studies (record numbers 052096, 052098, and 052099) (Chernoff, 8/29/89).

004 052097 Supplement to 52098 and 52099. "Teratology Study (Seg II) in Albino Rats with Phosphamidon (Dose Range-Finding Study)", (Science Applications, Inc., La Jolla, CA., 1/11/85), Phosphamidon Technical 91.8% purity, lot # FL831147, administered by gavage, 8/level, on days 6 through 15 of gestation (presence of vaginal smear or plug = 0) at 0 (0.2% CMC), 2, 4, 8, or 12 mg/kg. All animals died at the 8 and 12 mg/kg levels by day 12 of gestation. Tremors and oral and perianal discharges at 2, 4, 8, and 12 mg/kg. Reduced maternal and fetal weight gain at 4 mg/kg. No adverse effects. Establishes NOEL. NOEL (maternal) < 2 mg/kg (clinical obs.), (developmental) $\geq$ 4 mg/kg. (Green 9/24/87 and Gee 10/16/87).

TERATOLOGY, RABBIT

** 004 052096 "Teratology Study (Seg II) in Albino Rabbits with Phosphamidon", (Science Applications, Inc., La Jolla, CA., 1/11/85), Phosphamidon Technical 91.8% purity, lot # FL821262, administered by gavage, 18/level, on days 6 through 18 of gestation (day of breeding = 0) at 0 (0.2% CMC), 1, 3, or 10 mg/kg. 1 death/level at 1, 3, and 10 mg/kg. Reduced weight gain at 10 mg/kg. No adverse effects reported. NOEL (maternal) = 3 mg/kg, (developmental) $\geq$ 10 mg/kg. Initially reviewed as unacceptable but upgradeable with submission of dosing solution analysis or records of preparation and retrospective analysis (Green, 9/24/87 and Gee, 10/16/87). The data provided in the report on the dosing solution (CDFA record no. 075500) are adequate to complete the study which has been upgraded to ACCEPTABLE status (Chernoff, 8/29/89).

004 052095 Supplement to 52096. "Teratology Study (Seg II) in Albino Rabbits with Phosphamidon (Dose Range-Finding Study)", (Science Applications, Inc., La Jolla, CA., 1/11/85), Phosphamidon Technical 91.8% purity, lot # FL821262, administered by gavage, 8/level, on days 6 through18 of gestation (day of breeding = 0) at 0 (0.2% CMC), 2, 4, 8, or 12 mg/kg. 3 deaths at 12 mg/kg. Reduced weight gain at 4, 8, and 12 mg/kg. No adverse effects reported. Establishes NOEL. NOEL (maternal) = 2 mg/kg, (developmental) $\geq$ 12 mg/kg. (Green, 9/24/87 and Gee, 10/15/87).

Teratology Summary: CDFA is in agreement with EPA Guidelines which conclude that Phosphamidon does not demonstrate any significant developmental toxic effects in rats and rabbits.

GENE MUTATION

024 071642, "L5178Y/TK+/- Mouse Lymphoma Mutagenicity Test," (Beilstein, P., CIBA-GEIGY LTD, Laboratory Study No. 821215, 12/20/83). Phosphamidon technical (C 570; LOT #: p13449; purity = 91.8%), at concentrations of 0 (vehicle = F10P media), 20.6, 41.3, 82.5, 165.0 and 330.0 nl/ml without S9 activation and 65.0, 130, 260, 520, 1040 or 247.2, 329.6, 439.5, 585.9 and 781.3 nl/ml with S9 activation (4 hour exposure) was tested *in vitro* for mutagenic effects (8 tubes/concentration for mutagenicity and 4 tubes/concentration for viability control) on L5178Y/TK+/- mouse lymphoma cells. Test results show no increase in forward-mutant colonies with C 570 in this study. **Unacceptable** (No repeat test without S-9, inadequate S9 concentration--needs justification for concentration used). (Kishiyama & Silva, 4/19/90).

** 025 071644, "*Salmonella*/Mammalian - Microsome Mutagenicity Test", (Dr. B. Ogorek, CIBA-GEIGY Limited, Laboratory Study No. 881382, 9/28/88). Phosphamidon technical (C 570; LOT #: op 709400; purity = 93.6%) was tested with and without S-9 at concentrations of 0

(distilled water), 313, 625, 1250, 2500, or 5000 µg/plate (limit test) in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 (3 plates/dose) for 48 hours. A repeat experiment was also performed. **No adverse effect indicated.** Mutagenic effects were not observed at any dose of phosphamidon with or without S-9. Positive controls produced the expected results. ACCEPTABLE. (Kishiyama & Silva, 4/23/90).

CHROMOSOME

024 071640, "Chromosome Studies on Male Germinal Epithelium of Mouse Spermatogonia", (CIBA-GEIGY Limited, Laboratory Study No. 850101, 11/26/85). Technical Phosphamidon (C 570; LOT #: op 311531; purity = 92.1%) was administered by gavage to NMRI-derived male mice at 0 (distilled water), 1.12, 3.35 mg/kg (12 mice/group) once/day for 5 consecutive days. The mice were killed on day 5, three hours after receiving an i.p. injection of 10 mg/kg colcemide. 100 metaphase figures/animal (8 animals/group assayed). A preliminary test was performed to determine the highest dosage of phosphamidon to be used in the definitive study (no data shown). There were inadequate details in the report for the tissue/cell preparation process. **No adverse effect indicated.** NOEL > 3.35 mg/kg (no significant mutagenic effects on spermatogonia were observed at any dose level). **These data are supplementary.** (Kishiyama & Silva, 4/18/90.)

024 076141, "Chromosome Studies on Male Germinal Epithelium of Mouse Spermatocytes", (CIBA-GEIGY Limited, Laboratory Study No. 850102, 2/3/86). Technical Phosphamidon (C 570; LOT #: op 311531; purity = 92.1%) was administered to male Tif:MAGF (SPF), NMRI-derived mice (12/group) at 0 (distilled water), 2.23 and 6.7 mg/kg on days 0, 2, 3, 5 and 9. Three days after the final dose and 3 hours after receiving an i.p. injection of 10 mg/kg colcemide, the mice were sacrificed. Drop-preparations were made of the testicular parenchyma for 8 mice/group (100 primary spermatocytes and 100 secondary spermatocytes were examined/mouse). There was an inadequate description of the cell preparation. **No adverse effect indicated.** NOEL > 6.7 mg/kg (no significant mutagenic effects to primary or secondary spermatocytes was observed in this study). **These data are supplementary.** (Silva, 4/18/90.)

025 071645, "Nucleus Anomaly Test in Somatic Interphase Nuclei of Chinese Hamster", (F. Strasser, Study Director; CIBA-GEIGY Limited, Laboratory Study No. 850103, 10/23/85). Phosphamidon technical (C 570; purity = 92.1%; LOT #: op 311531), used in a modified micronucleus assay, was administered by gavage (single dose on 2 consecutive days) at 0 (distilled water), 1.675, 3.35 and 6.7 mg/kg to 6 random outbred Chinese Hamsters/sex/group--only 3/sex/group were scored, however. A preliminary test was done to determine optimal dose-range. Animals were sacrificed 24 hours after the second administration. Bone marrow smears were examined for nuclear anomalies. 1000 bone marrow cells/animal were scored for the following: a) Single Jolly bodies, b) fragments of nuclei in erythrocytes, c) micronuclei in erythroblasts, d) micronuclei in leucopoietic cells, e) polyploid cells. Cyclophosphamide (128 mg/kg dissolved in distilled water) was used as the positive control. **No adverse effect indicated.** One female animal at 6.7 mg/kg died, however there was no increase in nuclear anomalies at any dose, when compared to control. The positive control functioned as expected. The Nucleus Anomaly Test is not required by FIFRA Guidelines, therefore these data are considered to be supplementary. (Kishiyama & Silva, 4/24/90).

025 071646, "Nucleus Anomaly Test in Somatic Interphase Nuclei in Chinese Hamster", (F. Strasser, Study Director; CIBA-GEIGY Limited, Laboratory Study No. 821210, 12/21/83). Phosphamidon technical (C 570; purity = 92.1%; LOT #: op 13449, ex Res. 160), used in a modified micronucleus assay, was administered by gavage (single dose on 2 consecutive days) at 0 (arachis oil), 2.5, 5.0, and 10 mg/kg in the 1st study and 3.54, 5.0, 7.10 and 10 mg/kg in the 2nd study to 6 random outbred Chinese Hamsters/sex/group (1st study) or 9/sex/group (2nd

study). The dose levels selected were justified by using 1/3 the oral LD50 as the highest dose (Chinese hamster = 31, or 20-36 mg/kg). Animals were sacrificed 24 hours after the second administration. Bone marrow smears were examined for nuclear anomalies. 1000 bone marrow cells/animal (3/sex/dose--1st study and 4/sex/dose--2nd study) were scored for the following: a) Single Jolly bodies, b) fragments of nuclei in erythrocytes, c) micronuclei in erythroblasts, d) micronuclei in leucopoietic cells, e) polyploid cells. Cyclophosphamide (128 mg/kg dissolved in arachis oil) was used as the positive control. **Possible adverse effect indicated.** In the 1st study, 7/24 animals (6 males & 1 female) at 10 mg/kg died. There was a significant increase in anomalies at $\geq$ 5 mg/kg ($p < 0.05$). In the 2nd study, 1 control male, 2 males at 3.54 , 1/sex at 5.0 and 4 males & 1 female at 10 mg/kg died. There was a significant increase in nuclear anomalies at $\geq$ 5.0 mg/kg. Although the data showed a significant effect in both tests, the response was very weak, while mortality was reasonably high. The report states that the nucleus anomaly test is more sensitive than the micronucleus test (Mutation Research, 53:216-217, 1978). In the micronucleus assay, the effects of clastogenic compounds upon erythroblasts are observed in polychromatic erythrocytes. The nucleus anomaly assay examines erythroblasts as well as erythropoietic and leucopoietic compartments. Unacceptable (not a FIFRA Guideline study). Not upgradeable. M. Silva, 4/24/90.

025 071647, "Sister Chromatid Exchange Study", (G. Hool, CIBA-GEIGY Limited, Laboratory Study #: 821211, 6/15/83). Phosphamidon technical (C 570; purity = 91.8%; LOT #: P13449) was administered by a single gavage at concentrations of 0 (arachid oil), 2.5, 5, or 10 mg/kg to 4, 4, 4, and 6 Chinese hamsters/sex/group, respectively for 24 hours. Animals were treated with phosphamidon 2 hours after a subcutaneous implantation of 5-bromodeoxyuridine (45 mg tablet of BUdR) was placed in the neck. Slides of bone marrow from 2/sex/group (25 cells/slide) were examined for SCE. **No adverse effect.** A significant increase in SCE's was not observed at any dose of phosphamidon. Positive control performed as expected. Not Acceptable (FIFRA Guidelines require 5 animals/sex/group to be analyzed. The number of cells/animal scored was inadequate.) Not upgradeable. (Kishiyama & Silva, 4/24/90).

Conclusion: An adverse effect was observed in the definitive nucleus anomaly test (071646), which was stated to be a very sensitive assay. There were no positive effects observed in the sister chromatid exchange assay (071647), however, an inadequate number of animals were tested and an inadequate number of cells were scored. In both tests cells from bone marrow smears were examined, however in 071646 actual clastogenic activity was observed due to phosphamidon. At the same dose, an increase in DNA repair replication was not observed. Due to the increase in nuclear anomalies observed in 071646, CDFA considers phosphamidon to have a **possible adverse effect for chromosome damage.**
Although no one of the above tests is acceptable in and of itself, sufficient data are available to evaluate the chromosome effects of phosphamidon. Therefore, taken collectively, 071645-47 can be used to fill the chromosome damage data gap. M. Silva, 7/13/90.

DNA DAMAGE

** **025 071643**, "*Saccharomyces Cerevisiae* D7/Mammalian-Microsome Mutagenicity Test In Vitro," (Arni, P., CIBA-GEIGY Limited, Laboratory Study No. 821214, 9/29/83). Phosphamidon technical (C 570; purity = 91.8%; LOT #: P 13449) was tested at concentrations of 0 (distilled water), 80, 400, 2,000, or 10,000 µg/ml (with and without S-9) for mutagenic effects on *Sacchromyces cerevisiae* strain D7. Exposure time was 16 hours. Five plates/dose were tested on 2 selected media. The assay was repeated 3 times with and without S-9. **Possible adverse effect:** increased gene conversions were observed in all tests with S-9 activation. ACCEPTABLE. (Kishiyama & Silva, 4/20/90).

** 026 071648, "Autoradiographic DNA-Repair Test on Rat Hepatocytes", (Dr. Th. Hertner,

CIBA-GEIGY Limited; Laboratory Study No. 881341, 10/11/88). Phosphamidon technical (C570 technical; purity = 93.6%; LOT #: op. 709400) was used on primary hepatocyte cultures (Tif: RAIf(SPF) male rats) at concentrations of 0 (vehicle = distilled water), 0.55, 0.166, 0.5, 1.5, 3 and 6 ug/ml (1st test) or 0, 0.03125, 0.0625, 0.125, 0.25, 0.5 and 1.5 ug/ml (in a 2nd test to confirm the 5 hour exposure on DNA damage). Cells (previously treated with [3H]-thymidine for 16-18 hours) were analyzed by autoradiography (50 cells/slide were examined for a total of 150 cells/dose). **No adverse effect.** Phosphamidon, under conditions of this study, gave no evidence of inducing DNA damage to rat hepatocytes. ACCEPTABLE. (Kishiyama & Silva, 4/24/90).

026 071649, "Autoradiographic DNA Repair Test on Human Fibroblasts", (Dr. E. Puri, CIBA-GEIGY Limited, Laboratory Study No. 821212, 6/2/83). Phosphamidon technical (C 570 technical; purity = 91.8%; LOT #: p. 13449) was used at concentrations of 0 (culture medium), 2, 10, 50, or 250 nl/ml to test for DNA-repair synthesis to human fibroblasts *in vitro* (exposure time = 5 hours). [^{3}H]-Thymidine was added along with the test compound. 4 slides/dose (50 cells/slide) were scored. **No adverse effect.** Phosphamidon, under the conditions of this study, gave no evidence of DNA damage to human fibroblasts. UNACCEPTABLE and not upgradeable (the study should have also been performed with metabolic activation). (Kishiyama & Silva, 4/26/90).

Conclusion: Although a positive effect was observed in yeast cells, there were no positive effects in rat hepatocytes, or in human fibroblasts. It is more important that effects were not observed in mammalian (especially human), when compared to yeast cells. CDFA does not consider phosphamidon to have an adverse effect for DNA damage. M. Silva, 7/13/90.

NEUROTOXICITY

** 024 071639, "Acute Delayed Neurotoxicity Study in Laying Hens" (CIBA-GEIGY Limited, Laboratory No. 831242, 1/23/86). Phosphamidon Technical (C 570; LOT# : p212361; purity = 92.1%) was administered by oral gavage at a concentration of 30 mg/kg to 12 Leghorn hens. A second administration was performed 21 days later and the hens were observed for another 21 day period. 10 hens treated with distilled water and 4 hens treated with tri-orthocresyl phosphate (TCOP) served as the respective negative and positive controls. **No adverse effect** (no morphological evidence of neurotoxicity with phosphamidon). ACCEPTABLE. (Kishiyama & Silva, 5/1/90).